CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

VERNOLATE

Chemical Code # 001987, Tolerance # 00240
SB 950 # 122

July 30, 1986
Revised 1/20/88, 11/2/89, 7/13/90

I. DATA GAP STATUS

Chronic toxicity, rat: No data gap, no adverse effect.

Chronic toxicity, dog: No data gap, no adverse effect.

Oncogenicity, rat: No data gap, no adverse effect.

Oncogenicity, mouse: Data gap, inadequate study, no adverse effect indicated.

Reproduction, rat: Data gap, inadequate study, possible adverse effect indicated.

Teratology, rat: No data gap, possible adverse effect.

Teratology, rabbit: No data gap, no adverse effect.

Gene mutation: No data gap, no adverse effect.

Chromosome effects: No data gap, possible adverse effect.

DNA damage: No data gap, no adverse effect

Neurotoxicity: No data gap, no adverse effect.

Toxicology one-liners are attached.

In one-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

Revised by G. Chernoff, 11/2/89, and C. Aldous, 7/13/90.

All record numbers through Document 240-034, Record 088526, listed by the Pesticide Registration Library as of July 6, 1990, have been rectified with those listed in the Toxicology Summary (Aldous, 7/13/90).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

026 063278, "2-Year Chronic Toxicity and Oncogenicity Dietary Study With Vernam Technical in Rats", (Stauffer Chemical Co., Farmington, CT, 9/14/87). Vernolate technical (97.3%) at 0, 20, 75 or 300 ppm in the diet of 70 Sprague-Dawley rats/sex/group (80/sex in the 300 ppm group) for 24 months; Satellite group of 10/sex/group sacrificed at 3 months and used to evaluate clotting factors. Interim sacrifice of 10/sex/group at 12 months. NOEL = 75 ppm (decreased body weight gain, alveolar histocytosis in males); No oncogenic effect reported, **no adverse effect reported. **ACCEPTABLE**. (J. Gee, 1/20/88)

CHRONIC TOXICITY, RAT

See combined rat study.

CHRONIC TOXICITY, DOG

**033 072781 Auletta, C. S., "A Twelve Month Oral Toxicity Study in Dogs with Vernam* Technical". Bio/dynamics, Inc., East Millstone, N.J., study # T-12940, 12/8/88. Vernam (vernolate) Technical, 97.4% purity, administered orally in gelatin capsules for 1 year at 0, 5, 20, and 100 mg/kg/day with 5 Beagle dogs/sex/group. NOEL = 5 mg/kg/day: the only indications of treatment effects extending down to the LEL of 20 mg/kg/day were slight increases in extent of hemosiderin deposition and extramedullary hematopoiesis in the spleen. At 100 mg/kg/day, there were several findings consistent with anemia and associated enhanced turnover of RBCs: findings included statistically significant decreases in hemoglobin levels, hematocrit, and RBC counts in both sexes; also consistently elevated platelet counts in males; enhanced degree of the above spleen effects; brown pigment accumulation in liver reticuloendothelial cells and in kidney tubular epithelium; and hypercellular sternal bone

marrow. Also, the high dose led to reduced body weights in both sexes (statistically significant in females only), and to significantly elevated liver weights in both sexes, as well as significantly increased spleen and kidney weights in females. Occasional axonal degeneration in cervical and lumbar spinal cord in both sexes was observed in 100 mg/kg/day males and females. Thus there was found a sharp increase in response between 20 and 100 mg/kg/day. **No adverse effects**. **Acceptable**. H. Green/C. Aldous, 7/13/90.

ONCOGENICITY, RAT

See combined rat study.

ONCOGENICITY, MOUSE

014 037772, "Lifetime Oral Study in Mice, Vernam Technical", (International Research and Development Corp., 4/13/79, study no T-6343). Vernam (Vernolate), technical, 96.6%, lot # 3905-37, fed at 0, 10, 30, and 100 mg/kg/day in the diet for 2 years; 60/sex/group with interim sacrifice of 10/sex/group at 12 months; nominal NOEL $\geq$ 100 mg/kg/day (HDT). **UNACCEPTABLE**, (no MTD used, diet analyses for last five months only presented in report.) **No adverse effect** indicated. (C. Aldous, 4/17/86 & 11/87)
EPA 1-liner: Minimum. Systemic NOEL > 100 mg/kg/day (HDT), oncogenic potential negative up to 100 mg/kg/day, ChE effects not determined.

008 943205, (1979, International Research and Development) Partial duplicate of 014 037772 (Appendix missing). (J. Schreider, 5/1/85)

019 055176, supplemental to #037772: "Six Week Range Finding Study in Mice." (International Research and Development Corporation, 7/10/76). Vernam tech., 96.6%, lot # 3905-37; fed in the diet to 5/sex/group at 20 (weeks 1-3) raised to 640 (weeks 4-6), 40, 80, 160 or 320 mg/kg/day, no negative control group; significant effect on body weight and food consumption

seen only after increasing dose to 640 mg/kg/day. Range-finding for 037772 to justify dose selection for the oncogenicity study. (J. Gee, 11/3/87)

REPRODUCTION, RAT

011 943207, "A Two-Generation Rat Reproduction Study with Vernam Technical", (1/27/83, Stauffer, T-10124). Vernam* [vernolate] technical, 98.3% by weight, lot EHC-0139-25; fed in the diet at 0, 20, 100, and 500 ppm; 15 males and 30 females per group; nominal NOEL = 100 for reproductive effects (increased incidence of dilated renal pelves, convoluted ureter at 500 ppm, especially in the second litter of each generation). Parental NOEL = 20 ppm (decreased body weight gain and decreased food consumption at 100 ppm). **UNACCEPTABLE** (no histology on parental animals, also not all rats received gross necropsies). **Possible ADVERSE EFFECTS** noted (renal variants). The renal variants were ascribed to the weight changes and were said to be in the range of historical controls. Note: response in 240-021, dated June 23, 1987, Appendix 1, indicates the tissues from the parental animals were saved and will be examined in 1988 with a report submitted to CDFA. At the time the histopathology on the P1 animals is reviewed, the significance of the urinary tract effect noted in the weanlings of the second litters should be re-evaluated. (J. Schreider, 5/2/85 and J. Gee, 11/3/87)

021 058552, supplement to 943297. Historical control data for total urinary tract variants from four studies conducted from 10/83 through 9/86 - no data from 1981-1982. The source and strain of rat are not identified. The data are not presented in terms of effects on renal pelvis and convoluted ureter. (J. Gee, 11/3/87)

021 058553, supplement to 943297. Composition of a composite of 9 lots of Vernam (not including the lot used in the reproduction study.) (J. Gee, 11/3/87)

012 020178, (1983, Stauffer) exact duplicate of 011 943207.

015 037777, (1983, Stauffer) exact duplicate of 011 943207.

TERATOLOGY, RAT

****032 071104** Meyer, L. S., and Gilles, P. A. "A Teratology Study in CD Rats with Vernam Technical", (ICI Americas Inc., Agricultural Products Group, Environmental Health Center, Farmington, CT., report # T-13033, 10/13/88), Vernam (vernolate) technical, 97.4% purity, administered by gavage on days 6-20 of gestation at 0 (corn oil), 1, 17, and 300 mg/kg/day to 27, 23, 25, and 27 Crl:CD(SD)BRVAF/Plus female rats per group. **Maternal NOEL =** 17 mg/kg/day (decreased bodyweight gain during early pregnancy, associated with diminished food consumption during that period. Slight, but statistically significant ($p < 0.01$) increased liver weights.) **Developmental NOEL =** 17 mg/kg/day (slightly reduced fetal weights, increased numbers of fetuses having skeletal anomalies of moderate to serious degree). **Possible adverse effect**: developmental effects could not necessarily be attributed to maternal toxicity. **Acceptable**. H. Green/C. Aldous, 7/10/90.

TERATOLOGY, RABBIT

240-015 037776, Bryan, J., Werchowski, K.M., Rodwell, D.E., and Mayhew, D. "Teratogenic Potential (Segment II) Oral Study in Rabbits with Vernam", (WIL Research Labs, April. 7, 1981). Technical grade Vernolate, lot CGB-2601, 97%, was administered to groups of 21-22 rabbits by oral gavage on days 6 through 21 of gestation at doses of 0 (corn oil vehicle control), 2, 20, and 200 mg/kg/day. **No adverse effects or toxicity were observed at any of the doses tested. Maternal and developmental NOEL = 200 mg/kg/day. The study was previously reviewed as unacceptable but possibly upgradeable with the submission of additional information (Aldous, 4/17/86). Some required information was provided in record nos. 059213

and 059214 (Gee, 11/3/87). Satisfactory supplemental information on pilot and tolerance studies was submitted in record nos. 074924 and 074925 (Chernoff, 11/1/89). Original notebook entries showing solution preparation steps, plus retrospective analysis of the original lot were provided in Record 240-037:088526. The latter data allow the study to be upgraded to **Acceptable**. Aldous, 7/10/90.

240-037 088526 [Addendum to Document #: 240-015, Record # 037776]. Christopher, S.S. "A retrospective analysis of Vernolate (VERNAM∗) Technical: Addendum to teratogenic potential (Segment II) oral study in rabbits with Vernam (T-10401)." ICI Americas Inc., Western Research Center, Richmond, CA., 4/30/90. Record contains copies of original lab notebook pages showing weights and volumes mixed for each day's dosing solutions. The nominal concentrations are correct. In addition, reserve sample (from the original lot, #4921-24-3) was prepared according to methods used by WIL Research Laboratory, to make to 2 replicates of each of the 3 dosing solution levels employed in the original study. Analyses indicated 107% to 127% of nominal (i.e., the NOEL could be potentially too conservative). These data permit an upgrade of the cited study to "acceptable" status, since this was the last item of information needed for an upgrade (see CDFA Rebuttal Response of 11/2/89). Aldous, 7/10/90.

008 943206, (1981, WIL) partial duplicate of 015 037776. (J. Schreider, 5/1/85).

023 059213-059214, supplemental to 037776. Contains test substance identification information and individual clinical observations and maternal necropsy record sheets.

015 037775, (1980, WIL, WIL-80120) stated to be the range-finding study for 015 037776 but does not include any data on a dose of 400 mg/kg/day as stated in the rebuttal in 023, dated July 14, 1987.

034 074924-074925, supplemental to 037776. Contains the results of a tolerance study with 2 rabbits dosed at 400 and 800 mg/kg/day, and a negative pilot teratology study with small groups of rabbits dosed at 0, 2, 20, and 200 mg/kg/day. (Chernoff, 11/01/89)

TERATOLOGY, MOUSE

015 037774, "Vernam Safety Evaluation by Teratological Study in the Mouse", (Woodard Research Corp., 4/28/67). Vernolate, technical 96%; fed in the diet at 0, 8, and 24 mg/kg/day, days 6 - 18. Maternal toxicity and developmental toxicity NOEL $\geq$ 24 mg/kg/day (HDT). **No adverse effect** indicated. **UNACCEPTABLE,** not upgradeable (doses too low, study design too limited). (C. Aldous, 4/17/86)

GENE MUTATION

011 943208, "Mutagenicity Evaluation of Vernam Tech CGB-2601 - Final Report", (Litton Bionetics, 10/77). Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100. Vernolate, 97% (see 023, #59214); Bacteria were tested at 0, 0.001, 0.01, 0.1, 1.0 and 5.0 ul/plate with and without rat liver activation, one trial, one plate per concentration. Also tested Saccharomyces cerevisiae strain D4. **No evidence of a mutagenic effect**. **UNACCEPTABLE** due to protocol, missing information. (J. Schreider, 5/3/85)

015 037778, (1977, Litton Bionetics) exact duplicate of 011 943208.

011 943209, "The Ames Mutagen Assay Tested Against Herbicide and Herbicide Combinations", (published in Soil Science **131**:44-47 (1981)). Ames assay with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100. Vernolate, no purity stated. Concentrations used not given, no repeat trial, test article added to agar after poured onto plates, others. **No adverse effect** reported, **UNACCEPTABLE**. (J. Schreider, 5/3/85)

011 943211, "Evaluation of Herbicides for Possible Mutagenic Properties", (published in J. Agr. Food Chem. **20**: 649-656 (1972)); vernolate was one of 110 herbicides tested in Salmonella strains for mutation in Ames assay. **No adverse effect** indicated. **UNACCEPTABLE**. (J. Schreider, 5/3/85)

024 059375, "Mutagenicity Evaluation in Salmonella Typhimurium - Salmonella typhimurium", (Stauffer Chemical Co., Farmington, CT). Salmonella typhimurium strains TA-1535, TA-1537, TA-98, TA-100; Vernam (Vernolate - 97.3%) tested at 0, 0.0375, 0.0750, 0.1500, 0.3000 & 0.6000 ul/plate with and without rat liver activation; TA-1537 and TA-98 also tested at 0.05, 0.10, 0.21, 0.42 & 0.83 ul/plate; Triplicate plates. **No adverse effect. Complete. **ACCEPTABLE**. (N. Hughett, 10/26/87 and J. Gee 11/2/87)

CHROMOSOME EFFECTS

025 060527, "Mutagenicity Evaluation in L5178Y Mouse Lymphoma Multiple Endpoint Test Cytogenetic Assay", (Stauffer Chemical Co., Environmental Health Center, Farmington, CT, 7/16/87). Vernam (97.3%) at 0, 0.05, 0.06, 0.07, 0.08 & 0.09 ul/ml without activation and 0, 0.06, 0.07, 0.08, 0.09 & 0.10 with activation. Treated for 4 hours, harvested at 12 hours, scored 100 cells/concentration for aberrations. **No adverse effect** indicated. Complete, **UNACCEPTABLE** (only one harvest time, non-activation positive control (EMS) was non-functional). (N. Hughett, 10/26/87 and J. Gee, 11/2/87)

****025 060527**, "Mutagenicity Evaluation in L5178Y Mouse Lymphoma Multiple Endpoint Test Cytogenetic Assay, Vernam, T-12891", (Stauffer Chemical Co., Environmental Health Center, Farmington, CT, 7/16/87). Vernam (97.3%) at 0, 0.05, 0.06, 0.07, 0.08 and 0.10 ul/ml without activation and 0, 0.005, 0.006, 0.007, 0.008, 0.009 or 0.010 ul/ml with activation (rat liver S-9, induced with Aroclor 1254). Cells treated for 4 hours, harvested at 28 hours. **Possible ADVERSE EFFECTS**: statistically significant increase in number of SCE’s at 0.08 and 0.10 ul/ml without activation, statistically significant increase in number of SCE’s at all

concentrations with activation. Complete, **ACCEPTABLE**. (N. Hughett, 10/21/87 & J. Gee 11/2/87)

Summary: Although there are conflicting findings in this test area, the tests measure different endpoints - chromosomal aberrations and sister chromatid exchange, the mechanism of which is not understood. There remains a potential for genotoxicity with vernolate.

DNA DAMAGE

012 020177, "Mutagenicity Evaluation in Bone Marrow Micronucleus, Vernam Technical, Report No. T-11821", (Stauffer, 5/30/84). Vernolate, Lot WRC 4921-24-6, 98.3% (see 021, # 058553 for purity); mouse micronucleus test with 5/sex/group given 0, 800, 1000 or 1200 mg/kg in a single dose by oral gavage. Groups were sacrificed at 24, 48 or 72 hours. Cyclophosphamide as positive control. Dose selection based on a pilot study. No animal weights or number of normochromatic cells included. **No adverse effect reported. **ACCEPTABLE** with minor variations. (J. Schreider, 5/3/85)

011 943210, "Mutagenicity Screening of Pesticides in the Microbial System", (published in Mutation Research **40**: 19-30 (1976)). Bacillus subtilis. Vernolate, no purity stated, was one of 166 pesticides tested in the rec assay. **No adverse effect** reported. **UNACCEPTABLE**. (J. Schreider, 5/3/85)

NEUROTOXICITY

014 037771, "Acute Delayed Neurotoxicity Study With Vernam Technical in Adult Hens, T-6488", (Stauffer Chem. Co, Richmond, CA, 5 Nov 1979). Vernolate, tech. 0 and 10 ml, twice orally (neat) at 21 day intervals. **No neurotoxic effects noted. NOEL = 10ml/kg (HDT). **ACCEPTABLE** and complete.

(C. Aldous, 11/5/79)

013 027076, (1979, Stauffer) duplicate of 014 037771; missing tables.

013 027078, (1979, Stauffer) identical to 013 027076.

013 027077, (1979, Stauffer) neuropathy findings for 013 027076-78.

008 943202, (1979, Stauffer) duplicate of 014 037771, missing majority of study data. (J. Schreider, 5/3/85)